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Abstract: Rationale and Objectives: To investigate if anisotropy at 2D Shear Wave Elastography (SWE) suggests malignancy and whether it correlates with prognostic and predictive factors in breast cancer. **Materials and Methods:** Study-group A of 244 solid breast lesions was imaged with SWE between April 2013 and May 2014. Each lesion was imaged in radial and anti-radial planes and the maximum elasticity E_{max}, mean elasticity E_{mean} and standard deviation SD were recorded and correlated with benign/malignant status and if malignant, to conventional predictive and prognostic factors. The results were compared to a study-group B of 968 solid breast lesions, which were imaged in sagittal and axial plane between 2010 and 2013.

Results: Neither benign nor malignant lesion anisotropy is plane dependent. However, malignant lesions are more anisotropic than benign lesions ($p \leq 0.001$). Anisotropy correlates with increasing elasticity parameters, BIRADS categories, core biopsy result and tumour grade. Large cancers are significantly more anisotropic than small cancers ($p \leq 0.001$). The optimal anisotropy cut-off threshold for benign/malignant differentiation of 150 kPa² achieves the best sensitivity (74%) with a reasonable specificity (63%).

Conclusions: Anisotropy may be useful during benign/malignant differentiation of solid breast masses using SWE. Anisotropy also correlates with some prognostic factors in breast cancer.

Anisotropy of solid breast lesions in 2D Shear Wave Elastography is an indicator of malignancy

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Dear Sir or Madam,

Please consider the attached paper for publication.

Thank you very much in advance!

Kind regards,

Katrin Skerl

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Abstract

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Materials and Methods: Study-group A of 244 solid breast lesions was imaged with SWE between April 2013 and May 2014. Each lesion was imaged in radial and anti-radial planes and the maximum elasticity E_{\max} , mean elasticity E_{mean} and standard deviation SD were recorded and correlated with benign/malignant status and if malignant, to conventional predictive and prognostic factors. The results were compared to a study-group B of 968 solid breast lesions, which were imaged in sagittal and axial plane between 2010 and 2013.

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Conclusions: Anisotropy may be useful during benign/malignant differentiation of solid breast masses using SWE. Anisotropy also correlates with some prognostic factors in breast cancer.

Keywords: Elastography, breast, breast cancer, ultrasound, Shear Wave Elastography

Introduction

Supersonic Shear Wave Elastography (SWE) is an ultrasound imaging modality which visualizes the elasticity of tissue. It was introduced by Bercoff et al. in 2004 [1] and has been in clinical use since 2009 [2]. During examinations the propagation speed of the shear wave is measured and the elasticity, represented as Young's Modulus E , is calculated as

$$E=3\rho c^2$$

where c is the propagation speed of the shear wave and ρ is the density of the tissue. Thus SWE is a quantitative measurement method. The elasticity is visualised as a colour map overlaying the grey-scale B-mode ultrasound image of the lesion. As the shear wave is induced by applying an acoustic radiation force, there is no need to move the transducer. A good inter-observer reproducibility can be achieved [2]. Furthermore, Berg et al. have shown that analysing the

Abbreviations

AD – anisotropic difference
(difference of the measurements in each plane)

AF – anisotropy factor (square of AD)

AUC – area under the curve
(statistic measurement to evaluate the diagnostic performance of a method)

E – Young's Modulus
(measurement unit of tissue elasticity)

E_{\max} – maximum elasticity

E_{mean} – mean elasticity

ROC – receiver operator characteristics (statistical tool to evaluate the diagnostic performance of a method)

ROI – region of interest

SD – standard deviation

SWE – Shear Wave Elastography
(used elastography technique in the paper)

quantitative elasticity of a lesion with SWE is useful for the differentiation of benign and malignant lesions [2] as malignant tissue is generally stiffer than benign tissue [3]. Berg et al. recommended the use of a cut-off threshold for the maximum elasticity, E_{\max} of 80 kPa for the optimal benign/malignant differentiation [2]. Evans et al. recommend a cut-off threshold for the mean elasticity, E_{mean} of 50 kPa [4].

Evans et al. obtain four SWE images per lesion; each two in two orthogonal planes [5]. Observation of anisotropy during routine SWE evaluation of breast lesions prompted this study. Although Ciurea et al. observed anisotropy in solid breast lesions in 2011 [6], to our knowledge there have been no publications on the evaluation of the anisotropy of solid breast lesions on SWE to date.

Anisotropy is found in normal breast tissue and breast lesions. Ductal carcinoma in situ (DCIS) is known to grow faster in the radial than anti-radial plane [7]. Furthermore collagen alignment has been shown to be prognostic in invasive breast cancer [8]. This suggests that detection of anisotropy in SWE could potentially help characterise lesions with ultrasound.

The aim of this study was to observe the frequency and directional characteristics of anisotropy at SWE in benign and malignant lesions and correlate anisotropy with prognostic and predictive factors in breast cancer.

Materials and methods

Study-groups

Study-group A comprised 244 solid lesions visible on ultrasound (78 benign, 166 malignant) in 243 patients (age range 17-92, mean 58) scanned in our clinic between April 2013 and May 2014. For each lesion four images were obtained; first two in the radial plane and then two in the anti-radial plane. As preliminary data from a sub-group of the study-group A (174 of the 244 lesions in study-group A) suggested that anisotropy in solid breast lesions is not plane dependent [9], another

study-group B of 968 solid breast lesions (306 benign, 662 malignant) in 949 patients (age 17-95, mean 57) was also evaluated. For this group, images had been obtained in two orthogonal planes unrelated to the radial plane. The lesions of the study-group B were evaluated between 2010 and April 2013. Some of the 968 lesions in study-group B were evaluated in previous studies investigating the diagnostic performance of SWE (53 lesions [5], 165 lesions [4]), its correlation with prognostic factors (101 lesions [10]), lymph node involvement (396 lesions [11]) and tissue subtypes (302 lesions [12]) and whether SWE stiffness suggests response to neoadjuvant chemotherapy (40 lesions [13]). However, anisotropy was not measured on any of the SWE examinations in any of the previous studies.

Only patients who underwent core biopsy or surgical excision were included. Women with BIRADS 3 lesions younger than 25 years old did not undergo biopsy or short term follow up in our institution. Further exclusion criteria did not apply. Ethical approval by the National Research Ethics Service guidance was not necessary for this retrospective study [14]. Written informed consent for research purposes was available according to standard procedure in our clinic.

Ultrasound device

All examinations were performed using the ultrasound device Aixplorer (SuperSonic Imagine, Aix en Provence, France). The probe that was used to acquire the greyscale and SWE images had a frequency range of 4 to 15 MHz, which gives at -6 dB an axial resolution of 0.3 to 0.5 mm and a lateral resolution of 0.3 to 0.6 mm.

Image evaluation

All images were obtained by observers with 5-20 years' experience in breast ultrasound and at least 3 months experience in the performance of SWE. All four images in the two orthogonal planes were evaluated using a region of interest (ROI) size of 2 mm positioned at the stiffest point of E_{mean} in

the lesion or the surrounding tissue Artefacts and areas without measured elasticity (black on the colour-map) were excluded. Each image plane was centred at the approximated centre of the lesion. The elasticity parameters E_{\max} , E_{mean} and standard deviation (SD) were measured. To evaluate the anisotropic behaviour of the lesions the two measurements of E_{mean} for each plane were averaged. To estimate the plane dependence the anisotropic difference (AD) of the estimations per plane in study-group A was calculated as

$$AD = \text{antiradial} - \text{radial} \quad (2)$$

To evaluate the general plane independent anisotropy of the lesion the anisotropy factor (AF) was calculated as the squared anisotropic difference:

$$AF = (\text{antiradial} - \text{radial})^2 \quad (3)$$

Study-group B was imaged randomly in sagittal and axial plane. Therefore a plane dependency could not be evaluated but the anisotropy factor:

$$AF = (\text{sagittal} - \text{axial})^2 \quad (4)$$

The results of these calculations were compared to the histological features. Furthermore the diagnostic performance of the anisotropic difference and the anisotropy factor were calculated. The gold standard was histology from core biopsy or surgery.

BIRADS classification of the grey scale images was performed by an experienced breast radiologist blinded to the SWE and histological findings.

Core biopsy results were classified as recommended by the NHSBSP in [15], which is: Category B1 - unsatisfactory or normal tissue; category B2 - benign tissue; category B3 - tissue of uncertain malignant potential; category B4 - suspicious tissue; category B5a - malignant tissue in situ; category B5b - invasive tissue; category B5c - not assessable.

Statistics

The Receiver Operator Characteristic (ROC) analysis and statistical analysis using the T-test was performed using IBM SPSS (IBM, Armonk, New York, USA).

The performance of the different thresholds was compared with web-based software using Chi-square test. The null hypothesis was rejected at a level of 5% ($p \leq 0.05$).

Results

Evaluation of the study-groups

The 244 lesions of group A comprised 78 benign lesions and 166 malignant lesions. Three hundred and six of the 968 lesions in group B were benign and 662 lesions, malignant. The distribution of histology of each group is shown in Table 1; the distribution of screen detected and symptomatic lesions is shown in Table 2. The ultrasound imaging and histological features are also shown in Table 2.

Plane dependency

To investigate any correlation of the anisotropy of solid breast lesions with the anatomic structure of the breast, the AD of study-group A was evaluated. Fig. 1 shows the distribution of lesions stiffer in the radial plane ($AD < 0$) and lesions stiffer in the anti-radial plane ($AD > 0$).

No plane dependency of anisotropy could be found in any of the lesions whether benign or malignant. This result was confirmed by ROC analysis (Fig. 2) with an area under the curve (AUC) of 0.49 for benign/malignant differentiation.

Anisotropy threshold

The anisotropic factor (AF) was calculated. The AF is plane independent and indicates the degree of anisotropy. In Fig. 2 the ROC analysis for the correlation of AF with benign/malignant-differentiation is shown. For comparison the ROC of the elasticity parameters E_{\max} and E_{mean} are also shown.

With an AUC of 0.67, the AF suggests malignancy. However, the diagnostic performance of the AF is not as good as E_{\max} or E_{mean} (AUC for both 0.81). Calculation of the Youden's index gives an optimal cut-off threshold of $\text{AF}=200 \text{ kPa}^2$. In Table 3 the diagnostic performance for different thresholds of AF around the calculated Youden's Index is shown.

A threshold of 150 kPa^2 yielded the best sensitivity with a reasonably good specificity. This result was confirmed analysing group B. The overall diagnostic performance of thresholds of $\text{AF}=200 \text{ kPa}^2$ and $\text{AF}=250 \text{ kPa}^2$ was identical in group A. However, in group B a cut-off value of $\text{AF}=250 \text{ kPa}^2$ yielded the best overall performance. ROC analysis was in agreement with these thresholds.

Correlation with source of referral

To evaluate the correlation of anisotropy and the source of the referral, groups A and B were subdivided into screen detected or symptomatic lesions, and further subdivided into benign and malignant lesions. The AF of each subgroup was averaged and evaluated.

Fig. 3 shows the averaged AF for all sub-groups in groups A and B.

In group A all sub-groups of symptomatic lesions are significantly more anisotropic than screen detected lesions ($p \leq 0.005$ for total and malignant, $p \leq 0.05$ for benign lesions). In study-group B the

1 results are similar for the sub-groups of all (total) and malignant lesions. However, symptomatic
2 benign lesions are not significantly more anisotropic than screen detected lesions ($p=0.4$).
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5 **Correlation with Ultrasound Imaging and elasticity characteristics**

6
7

8 The dependence of anisotropy on the size of the lesion (ultrasound diameter) and the elasticity
9 parameters (E_{\max} , E_{mean} and SD) was evaluated. Therefore the lesions of group A and B
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11 dichotomised according to a threshold for each parameter, identified from the literature [2, 5, 16] as
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13 follows: that is an ultrasound diameter of 15 mm, E_{\max} of 80 kPa, E_{mean} of 50 kPa and a SD of
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15 7 kPa. Furthermore the sub-groups were divided into all (total), benign and malignant lesions. The
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17 results are shown in Fig. 4.
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24 Overall, large lesions (≥ 15 mm) are significantly more anisotropic than small lesions (< 15 mm)
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26 ($p \leq 0.001$). In particular, large malignant lesions are significantly more anisotropic than small
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28 cancers ($p \leq 0.001$). However, this correlation is not significant for benign lesions and may even be
29
30 independent of lesion size when the results in group B are considered.
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34 A very strong correlation between anisotropy and the elasticity parameters E_{\max} and E_{mean} was
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36 found ($p \leq 0.001$ for all sub-groups in groups A and B). However, in the sub-groups below and above
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38 the threshold the AF of benign and malignant lesions are similar. In group A, benign lesions with
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40 high elasticity were even more anisotropic than malignant lesions of high elasticity. However, this
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42 was not observed in group B.
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Anisotropy also correlates with the elasticity parameter SD ($p \leq 0.001$ for the sub-groups of all and benign lesions). The correlation with SD in the sub-group of malignant lesions was non significant in group A, but significant in group B ($p \leq 0.001$), which is probably due to a greater number of cases in group B. For the sub-groups with $SD < 7$ kPa, - malignant lesions are significantly more anisotropic than benign lesions ($p \leq 0.05$). However, all lesions of group A with $SD \geq 7$ kPa are in the same range and a difference of AF in benign and malignant lesions was seen only in group B ($p \leq 0.001$).

Correlation with ultrasound BIRADS

Groups A and B were divided into subgroups by ultrasound BIRADS categorisation. Furthermore the subgroups were divided into benign and malignant lesions. The averaged AF of each sub-group was correlated with ultrasound BIRADS categories (Fig. 5).

A correlation of the averaged AF and ultrasound BIRADS categories was observed. Overall lesions categorised as BIRADS 3 are less anisotropic than BIRADS 4a lesions (significant in group A with $p \leq 0.05$; not significant in group B, $p \leq 0.1$) and BIRADS 4a lesions are significantly less anisotropic than BIRADS 4b lesions ($p \leq 0.05$ for both groups). The difference in the averaged AF of benign and malignant lesions is non significant in BIRADS 3 as the number of malignant cases was low (one case) and significant in BIRADS 4a lesions ($p \leq 0.001$).

Correlation with core result

Groups A and B were subdivided according to the core biopsy result. The averaged AF was then correlated with results of core biopsy (Fig. 6).

The AF correlates with the core result; in general a more anisotropic lesion is more likely to be malignant. Lesions with a core result of B1, B2 or B3 are significant less anisotropic than lesions

with a core result of B5a ($p \leq 0.001$ in both groups). Furthermore B5b lesions are more anisotropic than B5a lesions ($p > 0.1$ in group A, $p \leq 0.001$ in group B).

Correlation with tumour grade

Malignant lesions in groups A and B were subdivided according to tumour grade and correlated with AF as shown in Fig. 7.

While the AF of lesions with a tumour grade of 2 and 3 are in the same range, lesions with a tumour grade of 1 are significantly less anisotropic ($p \leq 0.001$ in both groups).

Correlation with other histological features

The averaged AF was correlated with the HER2, PR and ER receptor status. There was no correlation found. Lesions with HER+/- had an AF of 21 vs. 23 $\text{kPa}^2/100$ in group A and 24 vs. 23 $\text{kPa}^2/100$ in group B. Lesions with ER+/- had an AF of 22 vs. 27 $\text{kPa}^2/100$ in group A and 24 vs. 22 $\text{kPa}^2/100$ in group B. Lesions with PR+/- had an AF of 24 vs. 21 $\text{kPa}^2/100$ in group A and 24 vs. 22 $\text{kPa}^2/100$ in group B.

Furthermore no correlation could be found with lymph node involvement (23 vs. 22 $\text{kPa}^2/100$ in group A; 25 vs. 23 $\text{kPa}^2/100$ in group B for lymph node positive/negative) nor vascular invasion (18 vs. 24 $\text{kPa}^2/100$ in group A; 26 vs. 23 $\text{kPa}^2/100$ in group B for vascular invasion positive/negative).

Correlation with subtypes

The benign and malignant lesions of groups A and B were divided into their subtypes. The averaged AF of each tissue subtype was calculated and is shown in Table 4. Mucinous and tubular carcinomas are less anisotropic than other malignant lesions while ductal carcinomas of no specific

type and lobular carcinomas are more anisotropic in both groups. A difference between group A and group B is visible which may be caused by the small numbers in each subgroup.

Discussion

We have shown that solid breast lesions are anisotropic at SWE assessment. Neither benign nor malignant lesions show consistent plane-dependent anisotropy; that is, elasticity may be greater in either radial or anti-radial plane regardless of the nature of the lesion. However, the degree of anisotropy represented by AF suggests malignancy. The optimal cut-off threshold for benign/malignant differentiation in group A, in whom elasticity was assessed in radial and anti-radial planes, was calculated to be 200 kPa^2 . A threshold of $\text{AF}=150 \text{ kPa}^2$ resulted in the best sensitivity with a reasonable specificity; if specificity is more important, a threshold of $\text{AF}=250 \text{ kPa}^2$ is preferable. These results were confirmed by analysing group B, where images were acquired in sagittal and axial planes.

Breast tissue is anisotropic in structure as the fibroglandular tissue is oriented along the ducts leading radially to the nipple. For ductal elongation local collagen fibre alignment is necessitated which leads to local mechanical anisotropy in the mammary gland [17]. Provenzano et al. have shown that the orientation of collagen fibres changes during tumour growth: first regions of dense collagen develop in the tissue, then the collagen fibres are aligned parallel to the tumour boundary while during further tumour growth, collagen fibres become reorganized orthogonal to the tumour boundary to enable invasion [18].

The higher anisotropy in the elasticity of malignant breast lesions may therefore correlate with the degree of invasiveness. Furthermore, the stiffest plane could suggest the growing direction of the tumour. This would also explain the higher anisotropy in invasive lesions. It is possible that the observed anisotropy in in situ lesions may correlate with the invasive potential of the lesion.

1 The anisotropy of solid breast lesions can also be evaluated with diffusion tensor magnetic
2 resonance imaging (DTI), which quantifies the directionality, if any, of diffusion of water
3 molecules in response to motion-probing local magnetic field gradients. In normal breast tissue,
4 water diffusion is anisotropic with a predominant vector towards the nipple (ie. along the radial
5 plane). Previous studies have shown that evaluating the anisotropy may be helpful for
6 benign/malignant differentiation [19 - 22]. They found malignant lesions more anisotropic than
7 benign lesions [19, 21] which is in agreement with our results.
8

9 Anisotropy was also evaluated by Sinkus et al. using magnetic resonance elastography (MRE) [23].
10 They found that anisotropy of solid breast lesions correlates with the degree of stiffness. However,
11 only two solid breast lesions (one fibroadenoma, one invasive ductal carcinoma) were included into
12 their study. Our results confirm and expand on their findings.
13

14 Our study does have some limitations. Groups A and B were subdivided and the AF was averaged
15 for each subgroup. However, evaluating the mean can be misleading if outliers are present
16 particularly in small subgroups.
17

18 SWE measurements were only made in two orthogonal planes. Therefore it is uncertain if the
19 stiffest plane of the tumour was measured, which may distort the results.
20

21 Furthermore the elasticity is calculated by the ultrasound system using equation 1, which is a
22 simplified equation and might hence influence the measurements. However, our aim was to
23 investigate anisotropy observed during clinical practice.
24

25 A further limitation is that this study was a single centre study, retrospective study, though care was
26 taken to minimise bias by blinding the observer to the final pathology of the lesions, and the
27 observer carrying out the greyscale BIRADS classification was not the one measuring the
28 anisotropy.
29

30 To our best knowledge this study is the first to investigate the significance of anisotropy of solid
31 breast lesions on SWE. The elasticity parameters should be investigated in further planes to enable
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the inclusion of the evaluation of the stiffest plane. Furthermore an investigation of the position of the lesion within the entire breast may be of interest.

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Figure Captions

Figure 1: Neither benign nor malignant lesions' stiffness is plane dependent. The distribution of lesions stiffer in the anti-radial plane (orthogonal to ducts) equals the distribution of lesions, which are stiffer in the radial plane (along ducts).

Figure 2: ROC curve of the plane dependent anisotropic difference (AD) and the plane independent anisotropy factor (AF) compared to the performance of E_{\max} and E_{mean} in group A. AD does not correlate with malignancy but AF. However, the diagnostic performance of AF is inferior to that of E_{\max} or E_{mean} .

Figure 3: Symptomatic lesions' stiffness is more anisotropic than screen detected lesions.

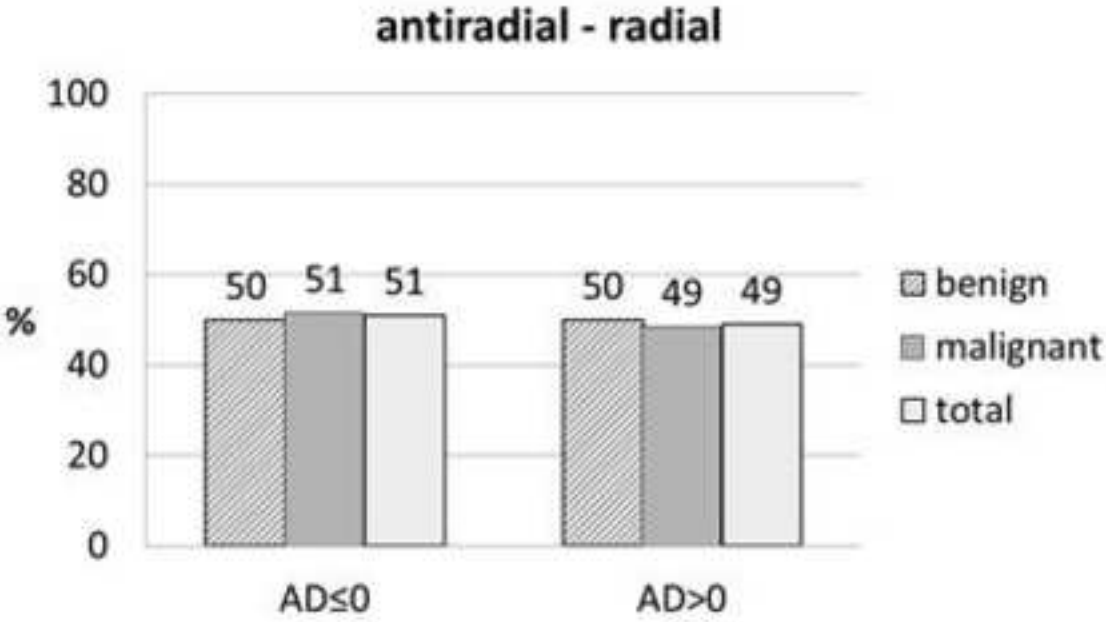
Figure 4: Larger lesions are more anisotropic on SWE than smaller lesions. Small benign lesions are less anisotropic than small cancers; large benign lesions are less anisotropic than large cancers. Furthermore, anisotropy on SWE correlates with stiffness (E_{\max} , E_{mean} , SD). There is no further correlation of AF with malignancy in soft or hard lesions.

Figure 5: BIRADS 3 and 4a lesions are less anisotropic on SWE than BIRADS 4b, 4c or 5 lesions. Malignant BIRADS 3 or 4a lesions are more anisotropic than benign BIRADS 3 or 4a lesions.

Figure 6: Anisotropy on SWE correlates with the result of core biopsy. Invasive cancers (B5b) are more anisotropic than in-situ cancers (B5a).

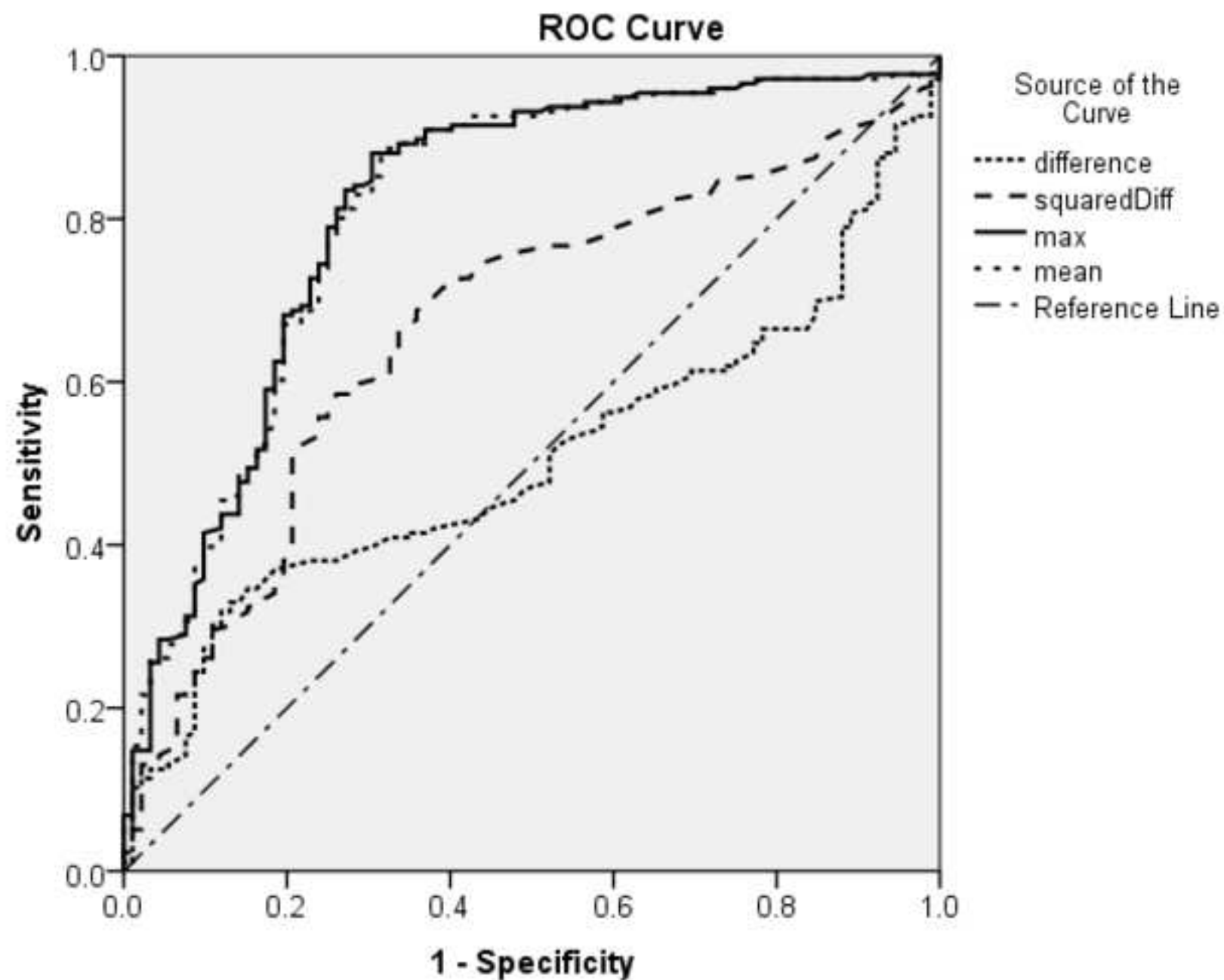
Figure 7: Tumours with grade 1 are less anisotropic on SWE than tumours with grade 2 or 3.

Figure
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Figure

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Diagonal segments are produced by ties.

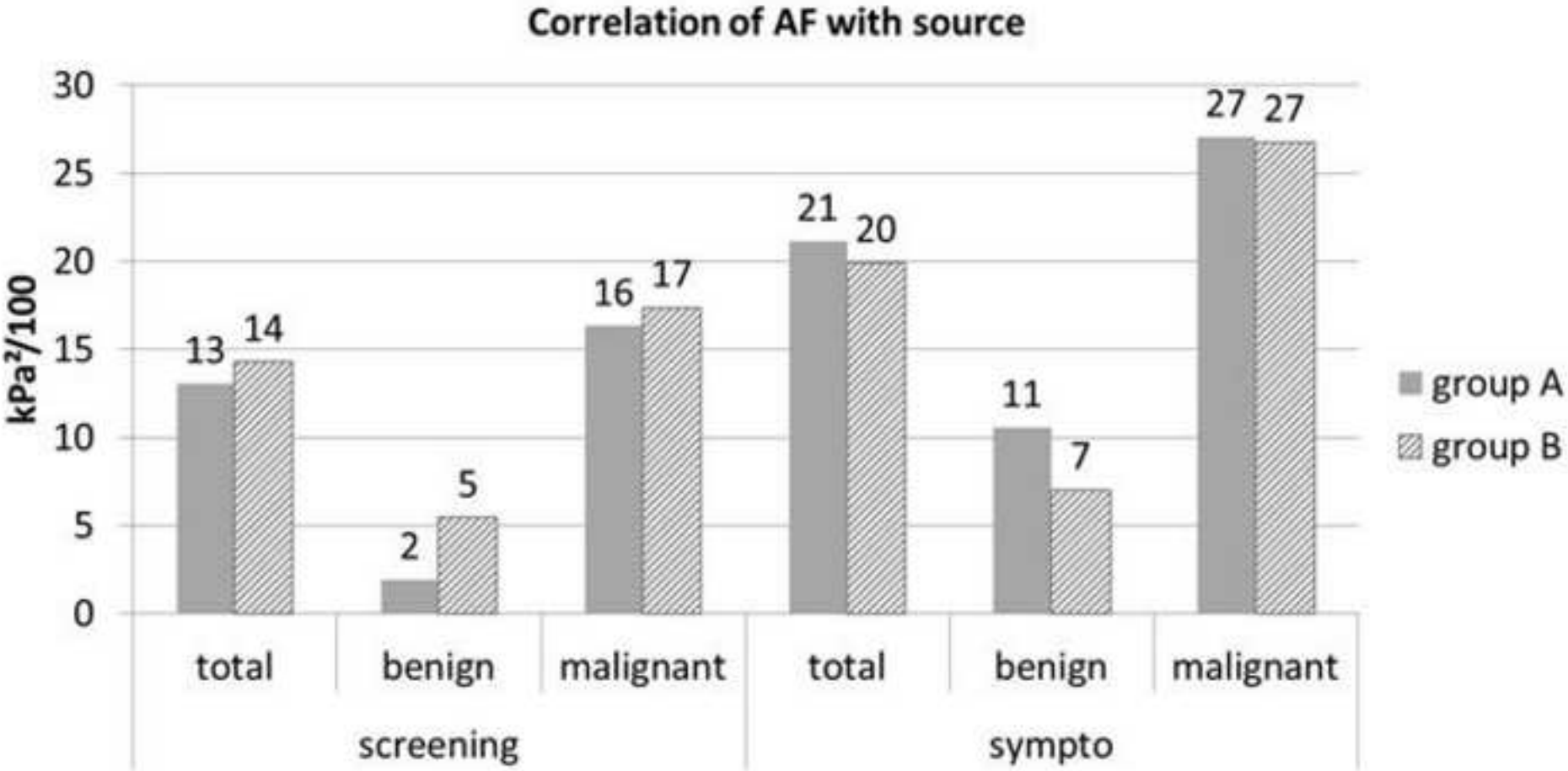


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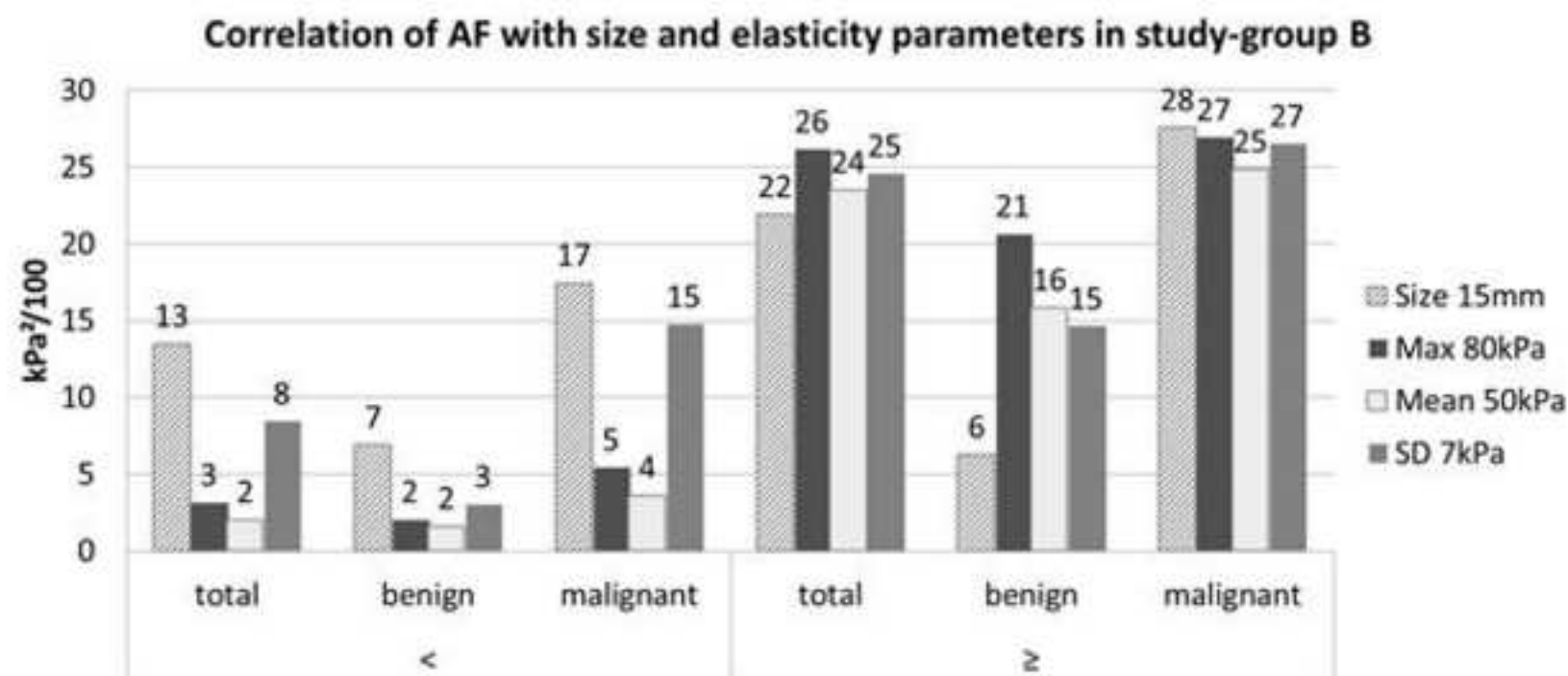
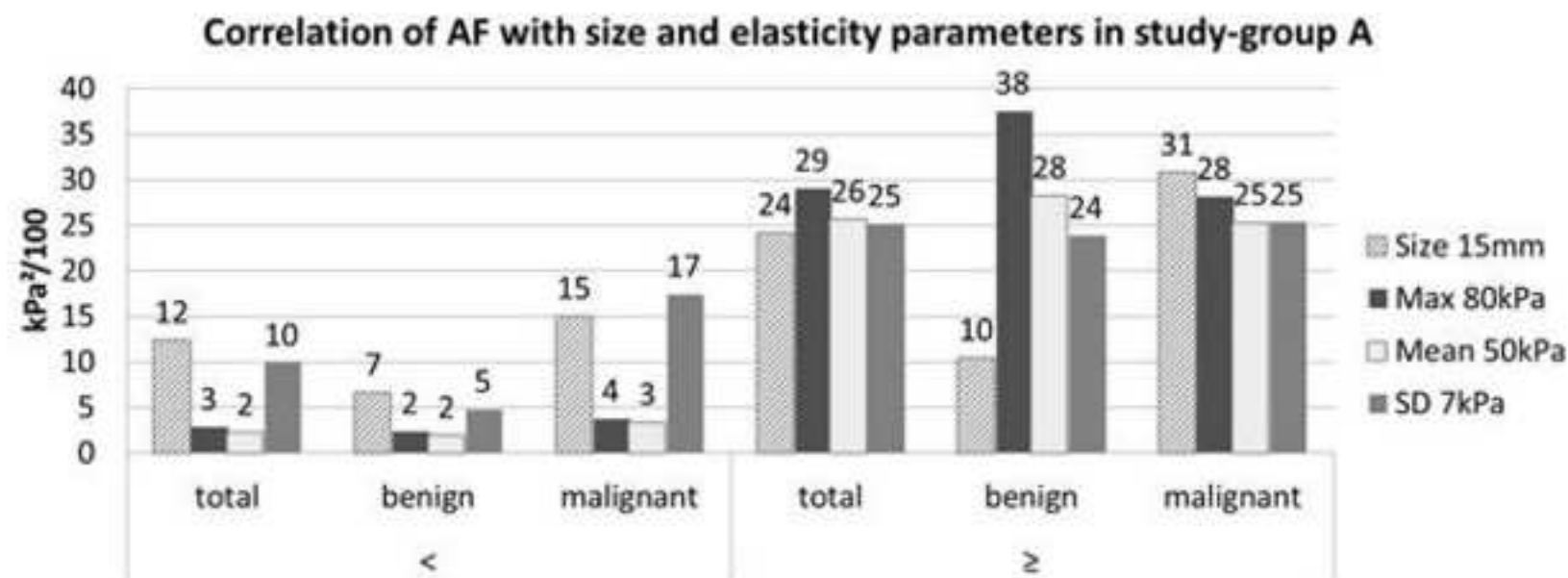


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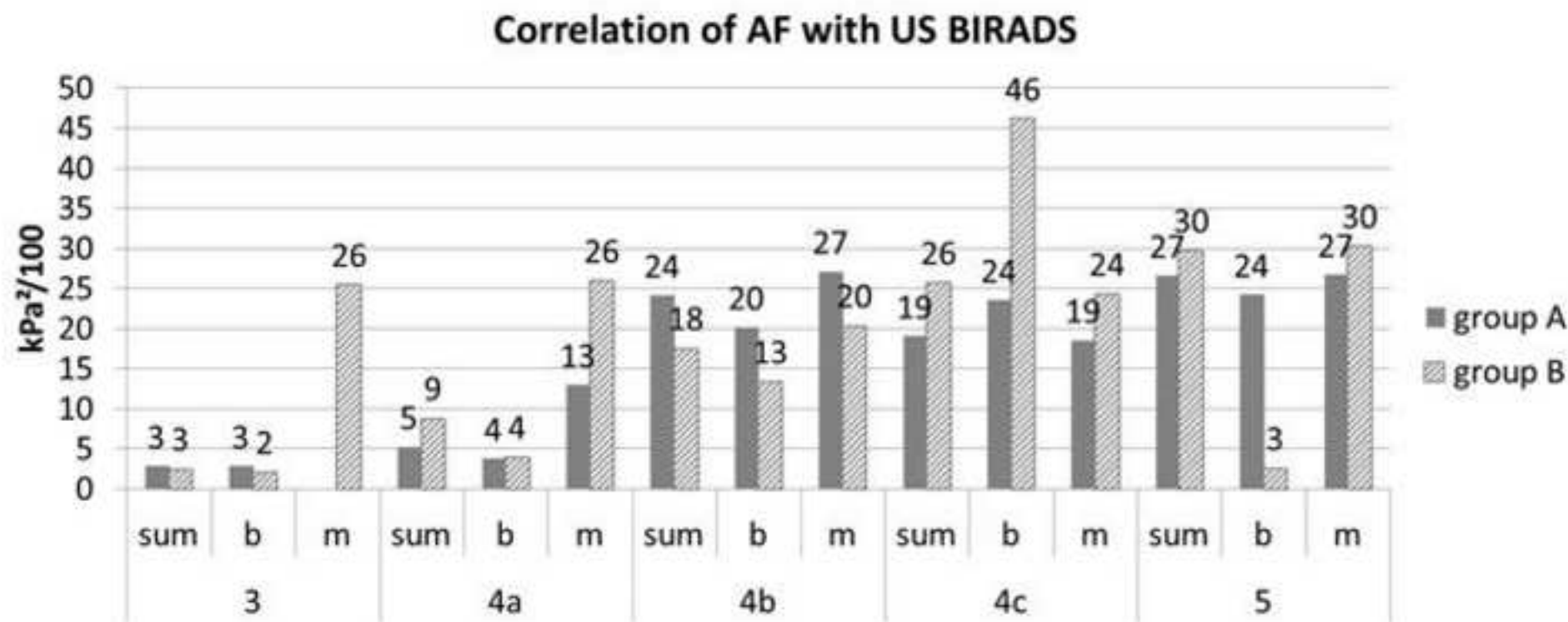
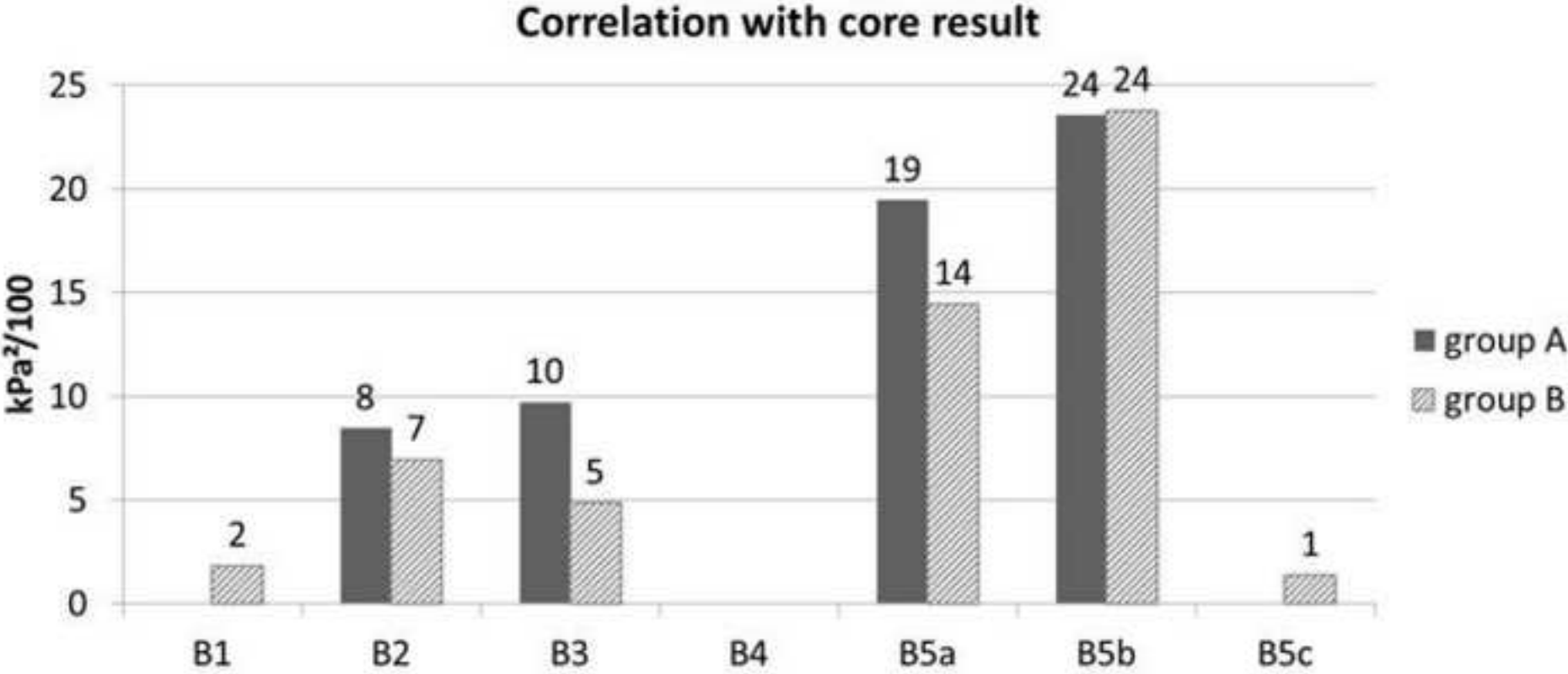
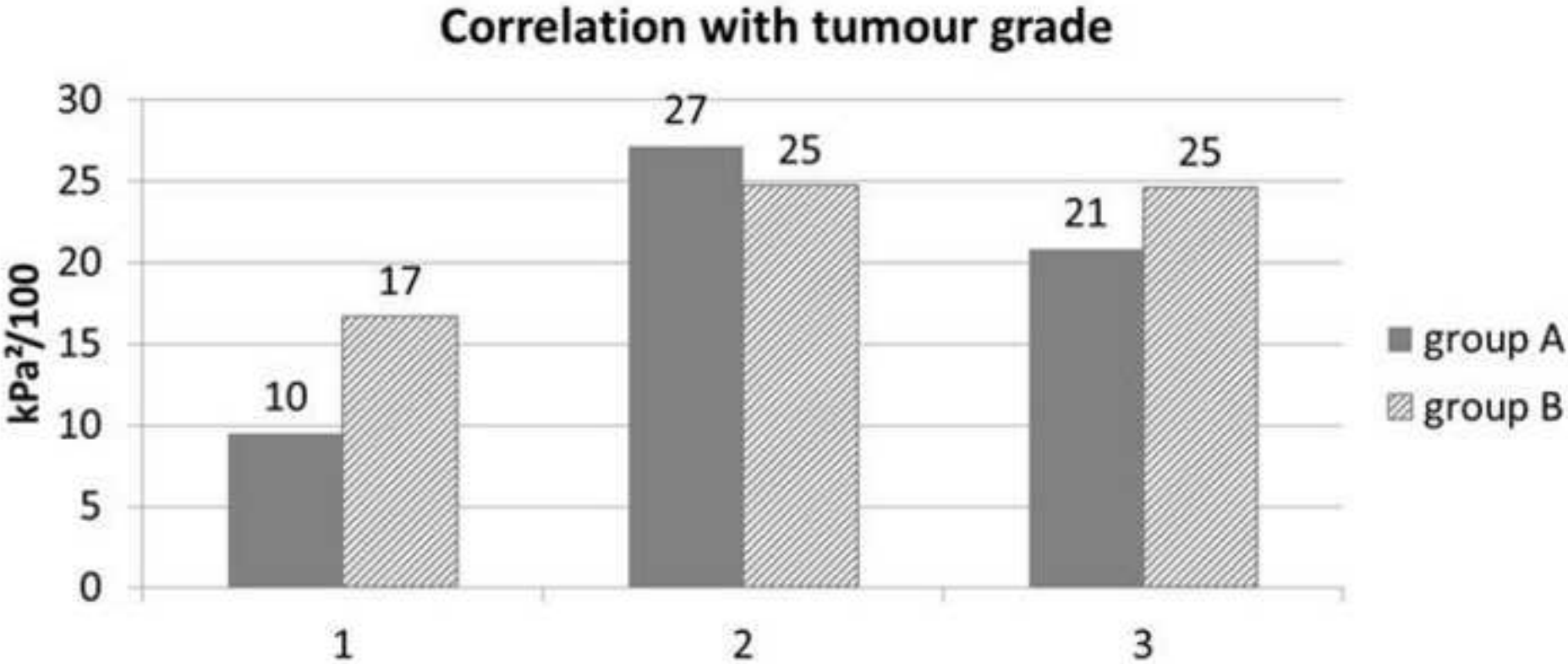


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Table

Subtype		study-group A		study-group B	
		number	%	number	%
Malignant	ductal carcinoma in situ	4	2	18	3
	ductal carcinoma of no specific type	110	68	482	76
	lobular carcinoma	34	21	78	12
	mucinous carcinoma	7	4	9	1
	tubular carcinoma	6	4	23	4
	papillary carcinoma	1	1	17	3
	Other	5	31	26	4
Benign	Fibroadenoma	43	69	148	55
	Fibrocystic changes	7	11	56	21
	Liponecrosis	3	5	15	6
	Papilloma	1	2	14	5
	Other	8	13	38	14

Table 1: Subtypes of solid breast lesions in the study-group A and study-group B

Feature		study-group A		study-group B	
		number	%	number	%
Source	screening	75	31	339	35
	symptomatic	170	69	629	65
Imaging	US size <15mm	115	47	454	47
	US size ≥15mm	130	53	514	53
	US BIRADS 3	34	14	53	11
	US BIRADS 4a	25	10	68	15
	US BIRADS 4b	28	11	88	19
	US BIRADS 4c	70	29	109	23
	BIRADS 5	88	36	152	32
	E _{max} <80kPa	97	40	336	35
	E _{max} ≥80kPa	148	60	615	65
	E _{mean} <50kPa	73	30	250	26
	E _{mean} ≥50kPa	172	70	717	74
	SD<7kPa	104	42	393	41
	SD≥7kPa	141	58	572	59
Histology	Core result B1	0	0	7	1
	Core result B2	70	29	261	27
	Core result B3	8	3	39	4
	Core result B5a	9	4	33	3
	Core result B5b	158	64	626	65
	Core result B5c	0	0	2	0
Characteristics of invasive cancers	HER2+	15	10	85	13
	ER+	136	83	522	81
	PR+	111	68	437	68
	Grade 1	15	9	71	11
	Grade 2	85	52	274	43
	Grade 3	65	39	289	46
	Lymph node positive	49	38	174	31
	Vascular invasion	40	31	156	28

Size, nodal status and vascular invasion were not available in those women treated initially with systematic therapy. HER status is missing in women with equivocal ELISA results who were not candidates for chemotherapy.

Table 2: Ultrasound assessment and histological features of the study-group A and the study-group B

Threshold	study-group A			study-group B		
	Se	Sp	DA	Se	Sp	DA
150	74	63	71	72	59	68
200	70	68	69	69	62	67
250	68	71	69	68	68	68

Table 3: Diagnostic performance of anisotropy factor (AF)

Subtype		study-group A	study-group B
		AF [kPa2/100]	AF [kPa2/100]
Benign	Fibroadenoma	5	4
	Fibrocystic changes	6	13
	Liponecrosis	42	4
	Papilloma	6	5
	Other	13	8
Malignant	ductal carcinoma in situ	26	7
	ductal carcinoma of no specific type	23	24
	lobular carcinoma	32	24
	mucinous carcinoma	5	11
	tubular carcinoma	7	15
	papillary carcinoma	2	32
	Other	17	22

Table 4: Correlation of AF with tissue subtype of the lesions of study-group A and B